



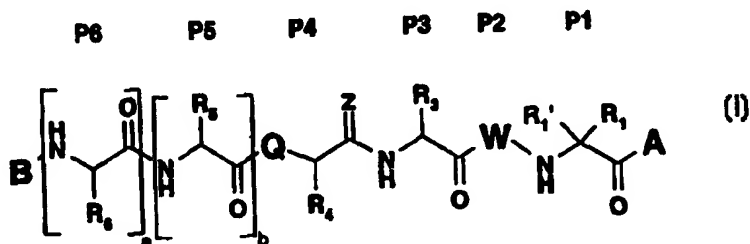
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(21) International Application Number: PCT/CA98/00765 (22) International Filing Date: 10 August 1998 (10.08.98) (30) Priority Data: 60/055,186 11 August 1997 (11.08.97) US (71) Applicant (for all designated States except US): BOEHRINGER INGELHEIM (CANADA) LTD. [CA/CA]; 2100 Cunard Street, Laval, Québec H7S 2G5 (CA). (72) Inventors; and (75) Inventors/Applicants (for US only): LLINAS-BRUNET, Montse [CA/CA]; 10543 Bélair, Pierrefonds, Québec H2V 2W8 (CA). POUPART, Marc-André [CA/CA]; 101 Aimé Séguin, Laval, Vimont, Québec H7M 1B3 (CA). RAN- COURT, Jean [CA/CA]; 6400 de l'Aiglon, Laval, Québec H7L 4W2 (CA). SIMONEAU, Bruno [CA/CA]; 2615 de la Volière, Laval, Québec H7N 5G3 (CA). TSANTRIZOS, Youla [CA/CA]; 1590 Champigny, Saint-Laurent, Québec H4L 4P7 (CA). WERNIC, Dominik [CA/CA]; 900 des Giroflées, Laval, Québec H7X 3G5 (CA). (74) Agent: VAN ZANT, Joan, M.; Van Zant & Associates, Suite 1407, 77 Bloor Street West, Toronto, Ontario M5S 1M2 (CA).			(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published Without international search report and to be republished upon receipt of that report.

(54) Title: HEPATITIS C INHIBITOR PEPTIDES

(57) Abstract

Compound of formula (I) active against the Hepatitis C virus, wherein when Q is CH₂, a is 0, b is 0 and B is an amide derivative; or when Q is N-Y wherein Y is H or C₁₋₆ alkyl, then B is an acyl derivative; R₆, when present, is C₁₋₆ alkyl substituted with carboxyl; R₅, when present, is C₁₋₆ alkyl optionally substituted with carboxyl; when Q is either CH₂ or N-Y, then Z is oxo or thioxo; R₄ is C₁₋₁₀alkyl, C₃₋₇ cycloalkyl or C₄₋₁₀ (alkylcycloalkyl); R₃ is C₁₋₁₀ alkyl optionally substituted with carboxyl, C₃₋₇ cycloalkyl or C₄₋₁₀ (alkylcycloalkyl); W is a proline derivative; R₁' is hydrogen, and R₁ is C₁₋₆ alkyl optionally substituted with thiol; or R₁ is C₂₋₆ alkenyl; or R₁' and R₁ together form a 3- to 6-membered ring; and A is hydroxy or a pharmaceutically acceptable salt or ester thereof.



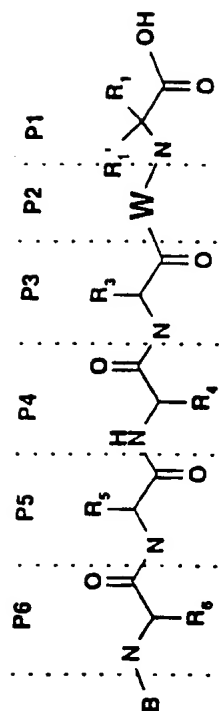
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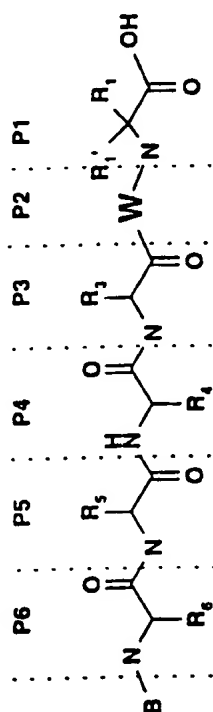
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- acetic acid); **Hyp**: 4(R)-hydroxyproline; **Hyp(4-Bn)**: 4(R)-benzyloxyproline; **Pip**: pipecolic acid (i.e. homoprolyl); **Tbg**: tert-butylglycine; **Ac**: acetyl; **Bn**: benzyl; **O-Bn**: benzyloxy; **DAD**: 3-carboxypropionyl; and
- 5 **DAE**: 4-carboxybutyryl; **AlGly**: allylglycine (2-amino-4-pentenoic acid); **thioxoIle**: L-thionoisoleucine; **Ph**: phenyl; **3I-Ph**: 3-iodophenyl; **4I-Ph**: 4-iodophenyl; **2Br-Ph**: 2-bromophenyl; **3Br-Ph**: 3-bromophenyl; **4Br-Ph**: 4-bromophenyl; **1-NpCH₂O**: naphthalen-1-ylmethoxy; 2-
- 10 **NpCH₂O**: naphthalen-2-ylmethoxy **3,5-Br₂Ph**: 3,5-dibromophenyl.

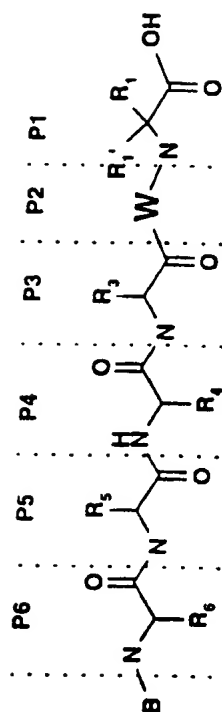
TABLE 1



Compound	B	P6	P5	P4	P3	W	P1	IC ₅₀ (μM)	HLE (μM)	PPE (μM)	Other (μM)	MS (MH ⁺)	AAA (%)
101	Ac	Asp	Asp	Ile	Val	Pro	Cys	46				703	113
102	Ac	Glu	Asp	Ile	Val	Pro	Cys	59				717	85.4 ± 1.6
103	DAD	---	Asp	Ile	Val	Pro	Cys	26				646	100.3 ± 1.8
104	Ac	Asp	D-Asp	Ile	Val	Pro	Cys	8.5				703	113.85 ± 4.9
105	Ac	Asp	D-Glu	Ile	Val	Pro	Cys	1.5				717	95.8 ± 0.8
106	Ac	Asp	Glu	Ile	Val	Pro	Cys	16*				717	98.8 ± 2.6
107	Ac	Asp	Val	Ile	Val	Pro	Cys	85*				687	85.9 ± 1.1
108	Ac	Asp	Tbg	Ile	Val	Pro	Cys	31				701	101.15 ± 1.65
109	Ac	Asp	Asp	Val	Val	Pro	Cys	80*				689	99.2 ± 5
110	Ac	Asp	Asp	Chg	Val	Pro	Cys	24*				729	102.95 ± 3.65
111	Ac	Asp	Asp	Tbg	Val	Pro	Cys	79				703	
112	Ac	Asp	Asp	Leu	Val	Pro	Cys	92*				703	109.7 ± 6.9
113	Ac	Asp	Asp	Ile	Ile	Pro	Cys	56*				717	72.4 ± 2.4
114	Ac	Asp	Asp	Ile	Chg	Pro	Cys	50*				743	103.65 ± 3.8
115	Ac	Asp	Asp	Ile	Val	Abu	Cys	58*				691	59.4 ± 2.85
116	Ac	Asp	Asp	Ile	Val	Leu	Cys	16*				719	95.4 ± 1.5

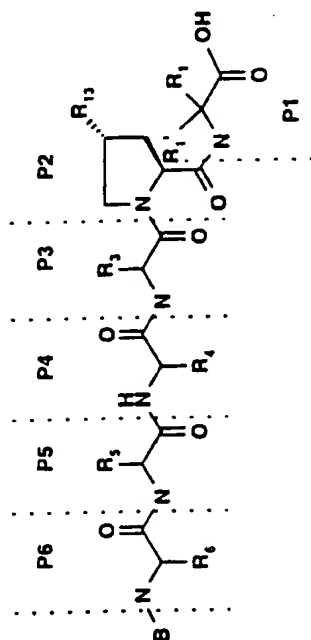


Compound	B	P6	P5	P4	P3	W	P1	IC ₅₀ (μ M)	HLE (μ M)	PPE (μ M)	Other (μ M)	MS (MH ⁺)	AAA (%)
117	Ac	Asp	Asp	Ile	Val	Phe	Cys	25*				753	99.6
118	Ac	Asp	Asp	Ile	Val	Val	Cys	133*				705	96.8 \pm 1
119	Ac	Asp	Asp	Ile	Val	Ile	Cys	90				719	87.0 \pm 3.0
120	Ac	Asp	Asp	Ile	Val	Ala	Cys	76*				677	N.S.
121	Ac	Asp	Asp	Ile	Val	Hyp(4-Bn)	Cys	1.7				809	101
122	Ac	Asp	Asp	Ile	Val	Pro	Abu	315				685	91.0 \pm 4.5
123	Ac	Asp	Asp	Ile	Val	Pro	Nva	220	>300	>300		699	107.6
124	Ac	Asp	Asp	Ile	Val	Pro	AlGly	210				697	106.3 \pm 8.2
125	Ac	Asp	Asp	Ile	Val	Pro	Acpe	210				711	94.02 \pm 3.19
126	Ac	Asp	Asp	Ile	Val	Pro	Acca	45				683	100.2
127	Ac	Asp	Asp	Ile	Val	Pip	Nva	605*				713	107
128	Ac	Asp	D-Glu	Ile	Val	Pro	Nva	7.4				713	100.9 \pm 3.6
129	Ac	Asp	Tbg	Ile	Val	Pro	Nva	270*				697	99.8 \pm 0.6
130	DAD	---	Asp	Ile	Val	Pro	Nva	123				642	107
131	Ac	Asp	Glu	Chg	Glu	Glu	Cys	24					
132	Ac	Asp	D-Glu	Chg	Glu	Glu	Acca	36					

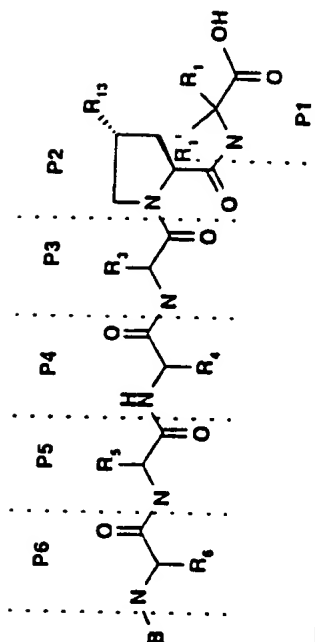


Compound	B	P6	P5	P4	P3	W	P1	IC ₅₀ (μM)	HLE (μM)	PPE (μM)	Other (μM)	MS (MH ⁺)	AAA (%)
133	Ac	Asp	Glu	Chg	Val	Glu(OBn)	Acca	39					

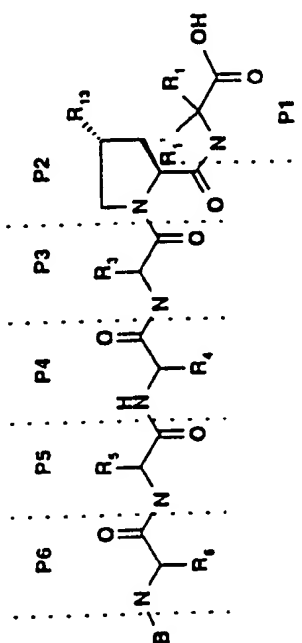
TABLE 2



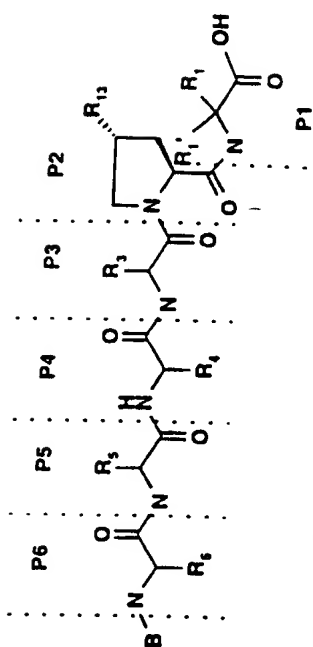
Comp.	B	P6	P5	P4	P3	R ₁₃	P1	IC ₅₀ (μM)	HLE (μM)	PPE (μM)	Other (μM)	MS (MH ⁺)	AAA (%)
201	Ac	Asp	Asp	Ile	Val	O-Bn	Nva	7.2				805	107
202	Ac	Asp	D-Val	Ile	Val	O-Bn	Nva	0.93				789	103
203	Ac	Asp	D-Glu	Ile	Val	O-Bn	Nva	0.6	>300	>300	>300**	819	96.3 ± 1.7
204	Ac	Asp	Asp	Ile	Val	<i>o</i> -tolyl- methoxy	Nva	9.4*				819	95
205	Ac	Asp	Asp	Ile	Val	<i>m</i> -tolyl- methoxy	Nva	6.7*				819	98.7
206	Ac	Asp	Asp	Ile	Val	<i>p</i> -tolyl- methoxy	Nva	6.4*				819	101.9
207	Ac	Asp	Asp	Ile	Val	1-NpCH ₂ O	Nva	0.39				855	112
208	Ac	Asp	Asp	Ile	Val	2-NpCH ₂ O	Nva	0.71				855	104
209	Ac	Asp	Asp	Ile	Val	4- <i>tert</i> -butyl- phenyl)- methoxy	Nva	2.6				861	114
210	Ac	Asp	D-Glu	Chg	Val	O-Bn	Cys	0.033	>300	>300	>300	849	101.7 ± 5.4



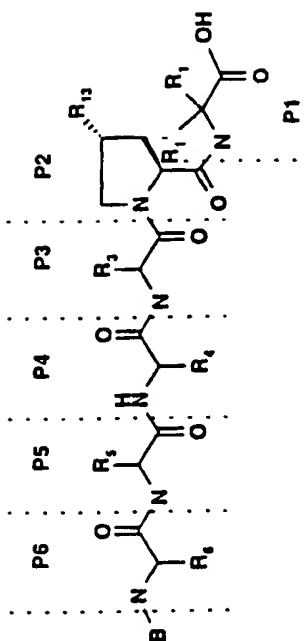
Comp.	B	P6	P5	P4	P3	R ₁₃	P1	IC ₅₀ (μM)	HLE (μM)	PPE (μM)	Other (μM)	MS (MH ⁺)	AAA (%)
211	Ac	Asp	D-Glu	Chg	Val	O-Bn	Nva	0.12				845	93.4 ± 2
212	Ac	Asp	D-Glu	Ile	Val	O-Bn	Acca	0.21	>300	>300		803	99.4 ± 2
213	Ac	Asp	D-Glu	Ile	Val	2-NpCH ₂ O	Nva	0.036				869	101.8
214	Ac	Asp	D-Glu	Chg	Val	2-NpCH ₂ O	Nva	0.028	>300	>300	>300 >300**	895	104.1
215	Ac	Asp	D-Glu	Chg	Val		Acca	0.014				879	---
216	Ac	Asp	Asp	Ile	Val	Bn	Nva	60				789	100.6 ± 0.8
217	Ac	Asp	Asp	Ile	Val	Ph(CH ₂) ₃ (Nva	3				818	94.6 ± 3
218	Ac	Asp	D-Glu	Ile	Val	O-Bn	Nva	0.49				910	111.2
219	Ac	---	Asp	Ile	Val	1-NpCH ₂ O	Nva	2.3				740	95.7
220	DAD	---	---	N(Me)Ile	Val	1-NpCH ₂ O	Nva	31				697	---
221	DAD	---	---	Ile	Val	1-NpCH ₂ O	Nva	22				683	---
222	DAE	---	---	Ile	Val	1-NpCH ₂ O	Nva	20				698	N.S.
223		---	---	Ile	Val	1-NpCH ₂ O	Nva	51				737	N.S.



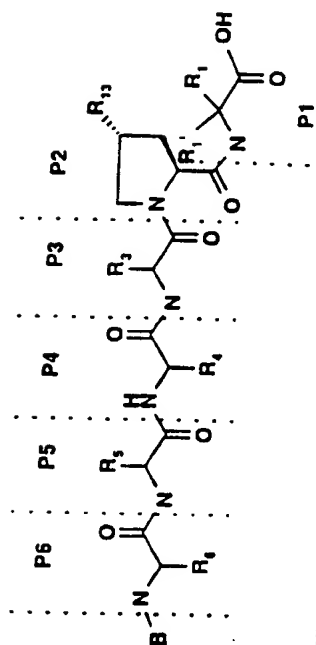
Comp.	B	P6	P5	P4	P3	R ₁₃	P1	IC ₅₀ (μM)	HLE (μM)	PPE (μM)	Other (μM)	MS (MH ⁺)	AAA (%)
224		---	---	Ile	Val	1-NpCH ₂ O	Nva	56				737	N.S.
225	Ac	---	---	Ile	Val	1-NpCH ₂ O	Nva	45				929	---
226	DAE	---	---	Chg	Val	1-NpCH ₂ O	Acca	0.76				707	---
227	Ac	---	---	Chg	Val	1-NpCH ₂ O	Acca	3	>600			635	
228	Ac	---	---	Chg	Val	O-Bn		35	>600			613.4	
230	Ac	Asp	Asp	Ile	Val	Ph(CH ₂) ₃	Nva	3.3				818	
231	Ac	---	---	Chg	Chg	1-NpCH ₂ O	Acca	2.6				675.4	
232	AcOCH ₂ -C(O)-	---	---	Chg	Chg	1-NpCH ₂ O	Acca	1.4					
233	Ac	Asp	Glu	Ile	Val	(3I- Ph)CH ₂ O	Acca	0.14				929.2	



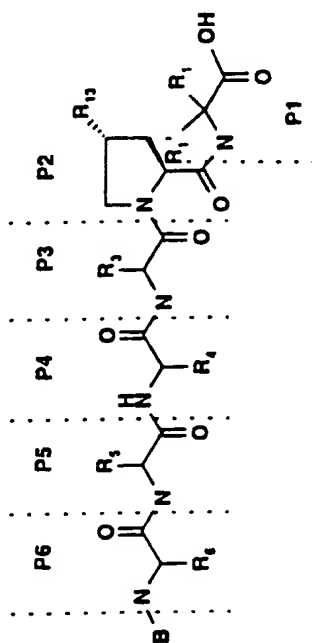
Comp.	B	P6	P5	P4	P3	R ₁₃	P1	IC ₅₀ (μM)	HLE (μM)	PPE (μM)	Other (μM)	MS (MH ⁺)	AAA (%)
234	Ac	---	---	Chg	Chg	O-Bn	Acca	41					
235	Boc	---	---	Chg	Chg	1-NpCH ₂ O	Acca	12					
236	Ac	---	Gly	thioxo-Ile	Val	1-NpCH ₂ O	Nva	4.0					
237	DAE	---	---	Ile	Val	1-NpCH ₂ O	Acca	5.5				720 (M+Na)	
238	Ac	---	---	Chg	Val	(4Br-Ph)O	Acca	27	195			598 (M+Na)	
239	Ac	---	---	Chg	Val	(2Br-Ph)O	Acca	27					
240	Ac	---	---	Chg	Val	(3Br-Ph)O	Acca	42					
241	Ac	---	---	Chg	Val		Acca	18					
242	Ac	---	---	Chg	Val	(4Br-Ph)S	Acca	36					
243	Ac	---	---	Chg	Val		Acca	35					



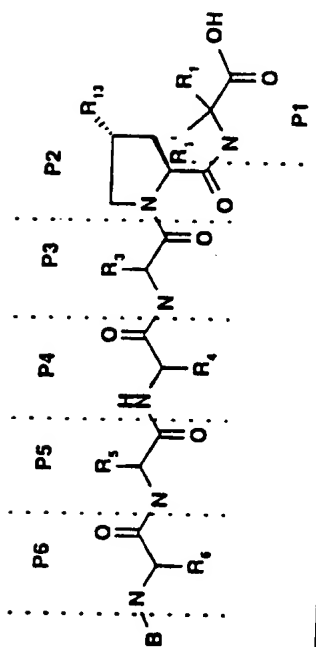
Comp.	B	P6	P5	P4	P3	R ₁₃	P1	IC ₅₀ (μM)	HLE (μM)	PPE (μM)	Other (μM)	MS (MH ⁺)	AAA (%)
244	Ac	---	---	Chg	Val		Acca	10					
245	Ac	---	---	Chg	Val		Acca	5.0					



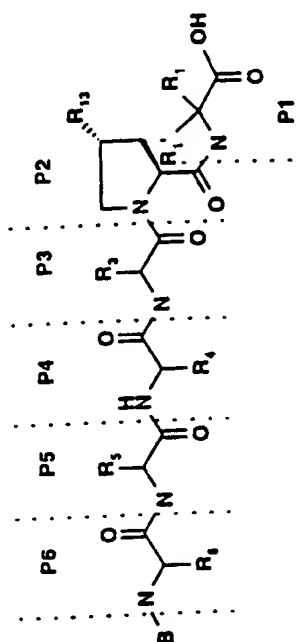
Comp.	B	P6	P5	P4	P3	R ₁₃	P1	IC ₅₀ (μ M)	HLE (μ M)	PPE (μ M)	Other (μ M)	MS (MH ⁺)	AAA (%)
246	Ac	---	---	Chg	Val		Acca	33					
247	Ac	Asp	Asp	Ile	Val	Ph(CH ₂) ₂	Nva	10					
248	Ac	---	---	Chg	Chg		Acca	3.6				803.6	119 \pm 1
249	Ac	---	---	Chg	Val	(4I-Ph)O	Acca	9.7					



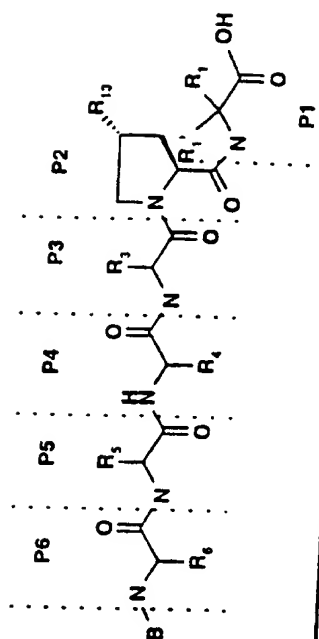
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250	Ac	---	---	Chg	Val		AcCa	4.5					
251	Ac	---	---	Chg	Val		AcCa	13					
252	Ac	---	---	Chg	Val	1-NpCH ₂ O	Nva	20				651.4	91±1
253	Ac	---	---	Chg	Val		AcCa	28					



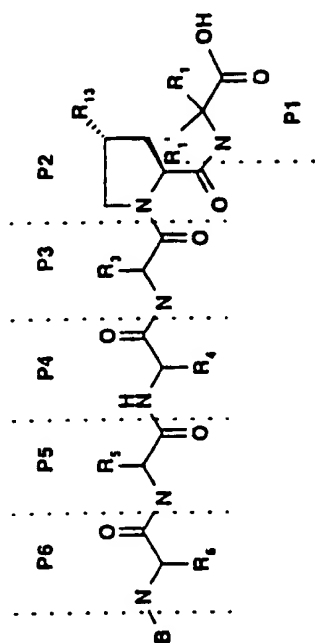
Comp.	B	P6	P5	P4	P3	R ₁₃	P1	IC ₅₀ (μ M)	HLE (μ M)	PPE (μ M)	Other (μ M)	MS (MH ⁺)	AAA (%)
254	Ac	---	---	Chg	Val		Acca	5.1					
255	Ac	---	---	Chg	Val		Acca	4.5					
256	Ac	---	---	Chg	Val		Acca	11					



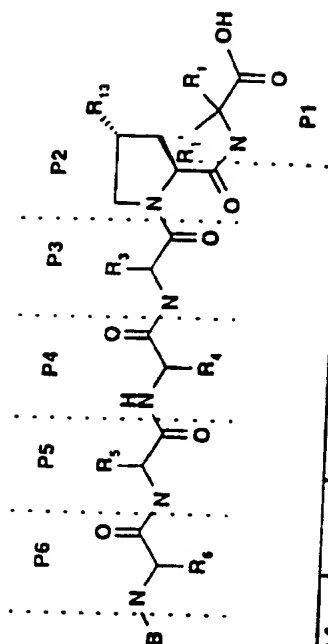
Comp.	B	P6	P5	P4	P3	R ₁₃	P1	IC ₅₀ (μM)	HLE (μM)	PPE (μM)	Other (μM)	MS (MH ⁺)	AAA (%)
257	Ac	---	---	Chg	Val		Acca	2.2	>300				
258	Ac	---	---	Chg	Val		Acca	16					
259	Ac	---	---	Chg	Val		Acca	28					
260	Ac	Asp	D-Glu	Ile	Val	O-Bn	Cys	0.18					
261	Ac	---	---	Chg	Val	O-Bn	Cys	28					
262	Ac	---	---	Ile	Val	1-NpCH ₂ O	Acca	40				631 (M+Na)	



Comp.	B	P6	P5	P4	P3	R ₁₃	P1	IC ₅₀ (μM)	HLE (μM)	PPE (μM)	Other (μM)	MS (MH ⁺)	AAA (%)
263		---	---	Ile	Val	1-NpCH ₂ O	AcCa	17				771 (M+Na)	
264		---	---	Ile	Val	1-NpCH ₂ O	AcCa	6.4				811	
265		---	---	Ile	Val	1-NpCH ₂ O	AcCa	10				811	
266		---	---	Ile	Val	1-NpCH ₂ O	AcCa	9.7				721.4	



Comp.	B	P6	P5	P4	P3	R ₁₃	P1	IC ₅₀ (μ M)	HLE (μ M)	PPE (μ M)	Other (μ M)	MS (MH ⁺)	AAA (%)
267		---	---	Ile	Val	1-NpCH ₂ O	Acca	12				721.4	
268	Ac	---	---	Chg	Val	(3Br-Ph)CH ₂ O	Acca	24				665.1	
269		---	---	Chg	Val	1-NpCH ₂ O	Acca	2.2				835.5 (M-H)	
270		---	---	Chg	Val	1-NpCH ₂ O	Acca	2.0				745 (M-H)	



Comp.	B	P6	P5	P4	P3	R ₁₃	P1	IC ₅₀ (μM)	HLE (μM)	PPE (μM)	Other (μM)	MS (MH ⁺)	AAA (%)
271		---	---	Chg	Val	1-NpCH ₂ O	Acca	3.8					
272	Ac	---	---	Chg	Val	(3,5-Br ₂ -Ph)CH ₂ O	Acca	27					
273	Ac	Asp	Asp	Ile	Val	H	Nva	17.5					
274	Ac	Asp	D-Val	Ile	Val	H	Cys	7.6					
275	Ac	---	---	Chg	Val		Acca	6.2					